WOUND LITERATURE COMPENDIUM

MicroMatrix® and Cytal® Wound Matrix in Clinical Practice

INTEGRA®

Table of Contents and Summary of Clinical Studies

Page	Title	Authors	Journal, Year	Study Type (N)	Wound or Injury Type	Subjects Treated with MicroMatrix and Cytal Wound Matrix	F/U Duration Reported Mean or Median
	ACUTE WOUND MANAGEMENT						
7	The Use of Urinary Bladder Matrix in the Treatment of Trauma and Combat Casualty Wound Care	Valerio IL et al	*Regenerative Medicine,* 2015	Retrospective review (N = 51)	Traumatic and combat wounds	51	24-42 months
9	Urinary Bladder Matrix Grafting: A Simple and Effective Alternative to Flap Coverage for Wounds in High-Risk Orthopedic Trauma Patients	Parry JA et al	*Journal of Orthopaedic Trauma,* 2022	Retrospective case series (N = 21)	Complex orthopedic trauma-related wounds	21	Not reported
11	Management of Open Distal Lower Extremity Wounds with Concomitant Fracture Using a Porcine Urinary Bladder Matrix	Kraemer BA et al	*Wounds,* 2016	Retrospective review (N = 9)	Open lower extremity fractures	9	18 months (minimum)
13	Management of Open Distal Lower Extremity Wounds with Exposed Tendons Using a Porcine Urinary Bladder Matrix	Geiger SE et al	*Wounds,* 2016	Retrospective case series (N = 13)	Open lower extremity wounds with exposed tendons	13	20 months (minimum: 13 months)
15	Extracellular Matrix Applications in the Treatment of Open Fractures with Complex Wounds and Large Soft Tissue Defects	Fokin AA et al	*Journal of Orthopedic Trauma,* 2018	Case series (N = 4; 5 injuries)	Open fractures with large soft tissue defects	4	3-12 months
17	Porcine Bladder Extracellular Matrix for Closure of a Large Defect in a Burn Contracture Release	Mitchell KB et al	*Journal of Wound Care,* 2012	Case study	Burn scar contracture involving the neck	1	16 weeks
	CHRONIC WOUND MANAGEMENT						
19	Evaluation of Tissue Engineering Products for the Management of Neuropathic Diabetic Foot Ulcers: an Interim Analysis	Frykberg RG et al	*Journal of Wound Care,* 2016	Prospective, randomized, comparative clinical trial (N = 95)	Diabetic foot ulcer	27	70 days
21	Urinary Bladder Matrix for the Treatment of Recalcitrant Nonhealing Radiation Wounds	Rommer EA et al	*Advances in Skin and Wound Care,* 2013	Retrospective case series (N = 3)	Nonhealing radiation wounds	3	18-24 months
23	Extending Limb Salvage After Fourth and Fifth Transmetatarsal Amputation in Diabetic Foot Infections Using ACell® Urinary Bladder Matrix	Underwood P et al	*The American Surgeon,* 2020	Retrospective case series (N = 2)	Diabetic foot infection following transmetatarsal amputation	2	3-6.5 months
25	A Value Analysis of Microsurgical Lower Extremity Reconstruction vs. Acellular Urinary Bladder Matrix (UBM) for Radiation Wounds of the Lower Extremity	Micallef CJ et al	*Journal of Surgical Case Reports,* 2019	Case study	Chronic leg ulcer following radiation therapy	1	2 years

Table of Contents and Summary of Clinical Studies (continued)

List of Abbreviations

3D: three-dimensional

ABx: antibiotics

Abd: abdominal

BKA: below-the-knee amputation

BMI: body mass index

DFI: diabetic foot infection

DFU: diabetic foot ulcer

DM: diabetes mellitus

FTSG: full-thickness skin graft

F/U: follow-up

Fx: fracture

HS: hidradenitis suppurativa

HTN: hypertension

IBD: inflammatory bowel disease

IED: improvised explosive device

IHD: ischemic heart disease

Integra® BWM: Integra Bilayer Wound Matrix

LE: lower extremity

LLE: left lower extremity

NPWT: negative pressure wound therapy

PG: pyoderma gangrenosum

PMHx: past medical history

Pts: patients

QoL: quality of life

RA: rheumatoid arthritis

Rad: radiation absorbed dose

S/P: status post

SOC: standard of care

STSG: split-thickness skin graft

TMA: trans-metatarsal amputation

UBM: Urinary Bladder Matrix

ECM: Extracellular Matrix

UE: upper extremity

WBC: white blood cell

The publications presented in this compendium contain the opinions of and surgical techniques practiced by the treating physician(s). The techniques are included in this document for informational purposes only. The decision of which techniques to use is the responsibility of the treating physician and depends on the patient profile, clinical situation, particular circumstances related to the procedure, and the physician's previous experience.

The authors of certain publications in this compendium may make claims that are not made by Integra LifeSciences or its representatives. In these publications, the use of Cytal Wound Matrix, MicroMatrix, and Integra Dermal Matrix devices fall within the current indications for the use of these devices.

Cases in this compendium involving Veterans Administration facilities or physicians do not reflect the opinion of the United States military or Veterans Affairs office.

Cytal Wound Matrix and MicroMatrix were previously marketed under the brand name MatriStem.

The Science of Urinary Bladder Matrix Devices

A Unique Platform Technology

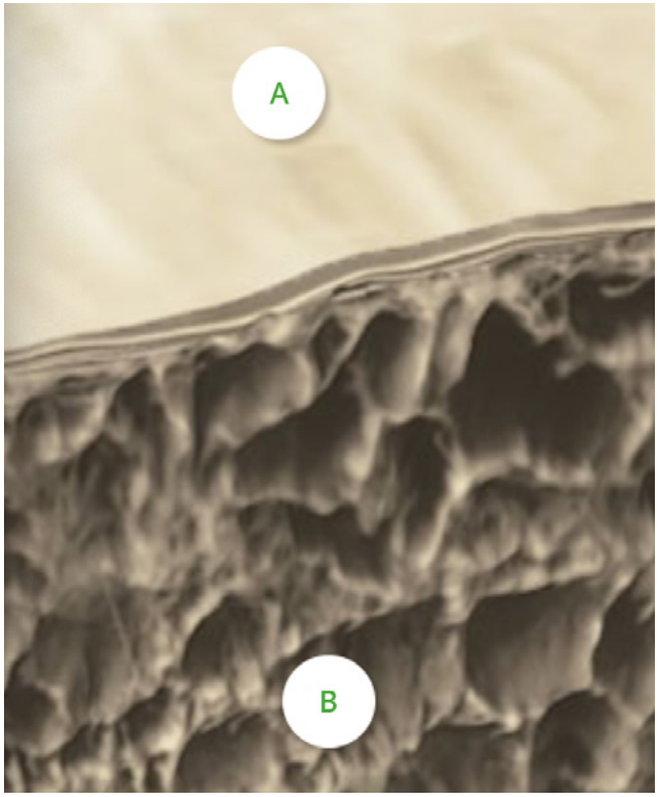
Proprietary UBM technology is used to manufacture Cytal Wound Matrix and MicroMatrix devices. This technology is **the only commercially available form of UBM.**

Product Design

Cytal Wound Matrix and MicroMatrix are **biologically derived and fully resorbable**.

The source material, porcine bladder, is minimally processed to remove cellular content and mitigate the inflammatory response. The manufacturing process preserves the integrity of essential structures and molecular components associated with wound healing.

These devices are **different from other ECM products** by virtue of having an intact epithelial basement membrane.



UBM DEVICES:
A 3D scaffold with 2 distinct layers:

- (A) Intact Epithelial Basement Membrane: a thin, dense structure that supports cell attachment and proliferation
- (B) Lamina Propria: a rough, porous structure that supports cellular infiltration and neovascularization

Cellular Responses to UBM

Following application, WBCs enter the UBM scaffold to initiate tissue remodeling. Fibroblasts migrate into the scaffold, depositing collagens that support new tissue growth. New blood vessels form, delivering blood and nutrients to the repair site.[1]

A higher ratio of M2:M1 macrophages has been documented within the UBM environment. This ratio facilitates the remodeling of **healthy, site-appropriate tissue.**[1,2]

Body of Evidence

UBM has an extensive body of research—including more than 100 preclinical and 50 clinical peer-reviewed publications. This compendium summarizes many clinically relevant articles in the area of wound management.

1. Brown BN, Londono R, Tottey S, et al. Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials. *Acta Biomaterialia.* 2012;8:978-987. **2.** Paige JT, Kremer M, Landry J, et al. Modulation of inflammation in wounds of diabetic patients with porcine urinary bladder matrix. *Regen Med.* 2019;14(4):269-277.

Acute Wound Manangement

The Use of Urinary Bladder Matrix in the Treatment of Trauma and Combat Casualty Wound Care

Valerio IL, Campbell P, Sabino J, Dearth CL, Fleming M; *Regenerative Medicine,* 2015.

Retrospective review (N = 51)

OBJECTIVE

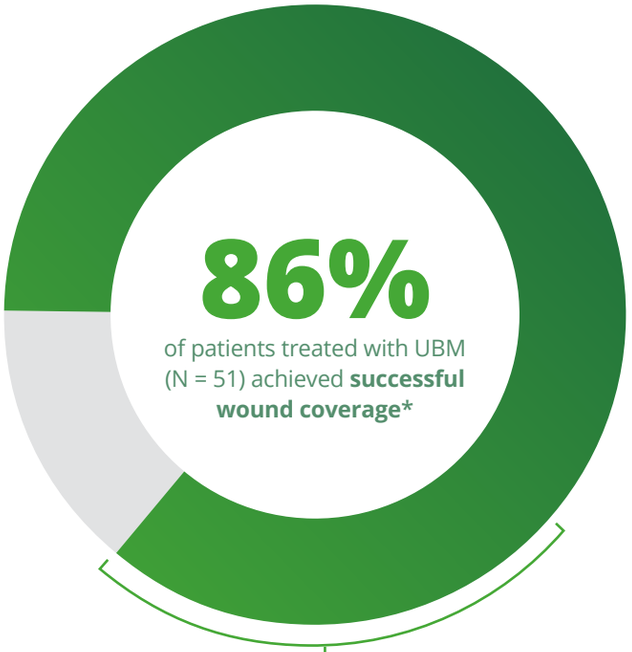
Evaluate the use of UBM with or without other devices, such as Integra Bilayer Wound Matrix in the treatment of traumatic and combat wounds where prior attempts to facilitate wound healing had failed

BACKGROUND

Challenges of traumatic and combat wounds

- **Soft tissue defects**
- **Stripped paratenon, periosteum, and perineurium**
- **High risk of infection**
- **Exposed joints**
- **Poor tissue perfusion**

RESULTS



In 32% of successful outcomes the surgeon used UBM and Integra BWM

Successful wound coverage with UBM was described as the development of a vascular bed suitable for re-epithelialization, Integra BWM, STSG, and/or tissue flap transfer

SUMMARY:

Benefits of MicroMatrix and Cytal (and/or Integra BWM) for traumatic wounds

- Facilitate vascularized tissue formation
- Prepare wound bed for re-epithelialization, BWM placement, or definitive wound closure
- Facilitate soft tissue reconstruction
- In contaminated wounds that had been cleaned and/or debrided, MicroMatrix and Cytal facilitated successful wound management
- UBM and Integra BWM can be used in combination or sequentially

Scan the QR code to read the full case study.

*UBM consisted of MicroMatrix powder or Cytal wound sheets used separately or concomitantly at the surgeon's discretion. Amount of product used and wound care regimen was also at the surgeon's discretion.

(continued)

The Use of Urinary Bladder Matrix in the Treatment of Trauma and Combat Casualty Wound Care

Valerio IL, Campbell P, Sabino J, Dearth CL, Fleming M; *Regenerative Medicine,* 2015.

WOUND CARE SUMMARY

Subjects

- All 51 pts had significant traumatic combat wounds
- Main mechanism of injury was IED blast
- Treated at Walter Reed National Military Medical Center

Initial Treatment

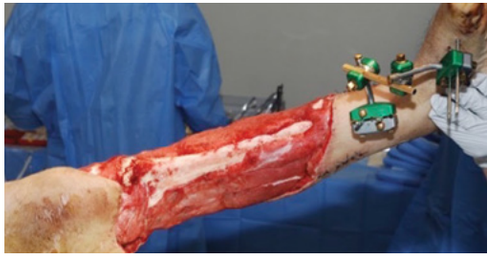
- All wounds were managed with UBM*
  - Irrigation and debridement
  - Application of MicroMatrix
  - Covered with Cytal, which was sutured in place

Ongoing Wound Management

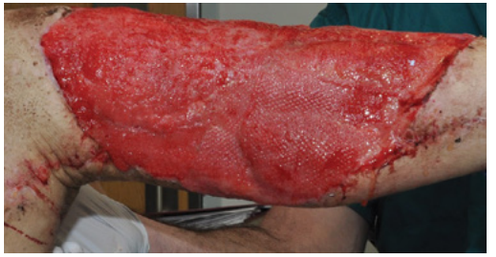
- Reapplication of MicroMatrix and Cytal every 3 days until formation of a healthy, vascularized wound bed
- Secondary coverage included Integra BWM, STSG, or tissue flap transfer
- 27% of pts managed with UBM and Integra BWM

ILLUSTRATIVE CASE STUDY

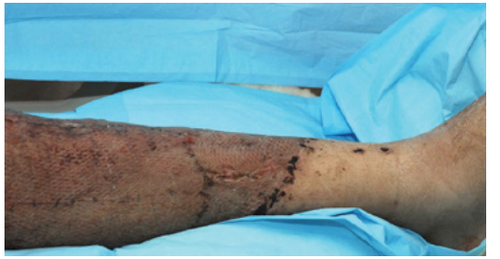
Successful outcome with MicroMatrix/Cytal:
27-year-old male with LLE blast-related trauma.



A. Gustilo-Anderson 3B LLE injury with severe degloving and exposed tibial fracture.



B. Free latissimus flap covers proximal 2/3, and MicroMatrix/Cytal scaffold covers the distal 1/3 of wound.



C. 1 month: STSG over hybrid reconstruction salvage and remodeled MicroMatrix/Cytal.

FOLLOW-UP

3 Years: The LLE reconstruction and salvage remained stable, with no breakdown. The patient, who also underwent a right BKA, was able to perform extreme athletic activities including monoskiing.

> “The incorporation of UBM derived ECMs in surgical treatment algorithms can facilitate achieving stable wounds, which leads to improved outcomes.”

KEY TAKEAWAYS

- Contributed to stable wound coverage in 86% of cases
- Helped patients resume activities of daily living
- Enabled reconstruction and/or limb salvage
- UBM and Integra BWM worked together to help achieve wound closure

*UBM consisted of MicroMatrix powder or Cytal wound sheets used separately or concomitantly at the surgeon’s discretion. Amount of product used and wound care regimen also was at the surgeon’s discretion.

Urinary Bladder Matrix Grafting: A Simple and Effective Alternative to Flap Coverage for Wounds in High-Risk Orthopaedic Trauma Patients

Parry JA, Shannon SF, Strage KE, et al. *Journal of Orthopaedic Trauma,* 2022.

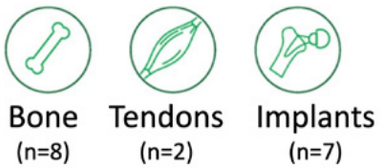
Retrospective case series (N = 21)

OBJECTIVE

To describe a technique for UBM grafting in orthopedic trauma and report results with this technique

SUBJECTS

- 21 patients with complex orthopedic wounds treated with UBM over a 2-year period*
- Reasons for UBM grafting
  - Not amenable to primary closure (n = 16)
  - Fasciotomy leg wound after failed skin graft (n = 1)
- Complicating factors
  - Active infection (n = 11)
  - Exposed structures:



SURGICAL TECHNIQUE

The authors suggest that UBM grafts be considered for wounds that cannot be closed primarily, even with infection or exposed bones, tendons, or implants

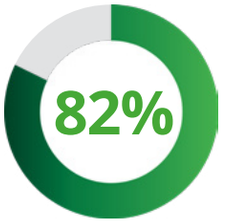
Debride
Remove all non-viable or infected tissue

Apply UBM Powder
Cover exposed structures in wound bed (if present) with MicroMatrix®†

Cover with UBM Sheet
Completely cover wound with a sheet of Cytal® Wound Matrix

Apply NPWT
Apply non-adherent mesh dressing and utlize negative pressure wound therapy (NPWT) for 2 weeks‡

OUTCOMES



Complete wound healing

14 of 17 patients achieved complete healing after primary UBM grafting

Reasons for initial non-healing (3/17)

- Error in early home-based wound care
- Graft failure over a fibular plate
- Suboptimal postoperative wound care in a homeless man with alcoholism

Complications (5/17)

- The 5 patients had 8 complications, requiring 9 revision procedures
- All wounds, including initial nonhealing wounds, eventually healed without the need for flap coverage

"Porcine UBM is a simple and effective alternative to flap coverage."

*Of the initial 21 patients, 4 were lost to follow-up and were excluded from the analysis.

† MicroMatrix® was mixed with saline to form a putty before application.

‡The safety and effectiveness of concomitant use of Cytal® and/or MicroMatrix® with NPWT has not been established or cleared by the FDA.

Urinary Bladder Matrix Grafting: A Simple and Effective Alternative to Flap Coverage for Wounds in High-Risk Orthopaedic Trauma Patients

Parry JA, Shannon SF, Strage KE, et al. *Journal of Orthopaedic Trauma,* 2022.

ILLUSTRATIVE CASE STUDIES

70-year-old man with a history of diabetes and gastric bypass surgery

A. Presented with an infected medial ankle wound dehiscence after medial malleolus fracture fixation.

B. UBM powder applied, then covered with a 3-layered UBM sheet. A non-adherent mesh dressing was applied, and patient underwent NPWT.

C. 4-Weeks. Robust granulation tissue present. NPWT discontinued.

D. 12-Months. Complete wound healing.

KEY TAKEAWAYS

- This series comprised orthopedic trauma patients with difficult-to-treat wounds
- Most procedures were successful despite patients having active infections or multiple comorbidities
- Many of the patients had exposed bones, tendons, or implants
- There was a high wound healing success rate (82%) with MicroMatrix® and Cytal® in wounds that would otherwise require flap coverage
- Flap procedures cannot always be performed in a timely manner. In contrast, wounds can be treated rapidly with MicroMatrix® and Cytal®

*Of the initial 21 patients, 4 were lost to follow-up and were excluded from the analysis.

†MicroMatrix® is mixed with saline to form a putty before application.

‡The safety and effectiveness of concomitant use of Cytal® and/or MicroMatrix® with NPWT has not been established or cleared by the FDA

Management of Open Distal Lower Extremity Wounds with Concomitant Fracture Using a Porcine Urinary Bladder Matrix

Kraemer BA, Geiger SE, Deigni OA, Watson TC; *Wounds,* 2016.

Retrospective review (N = 9)

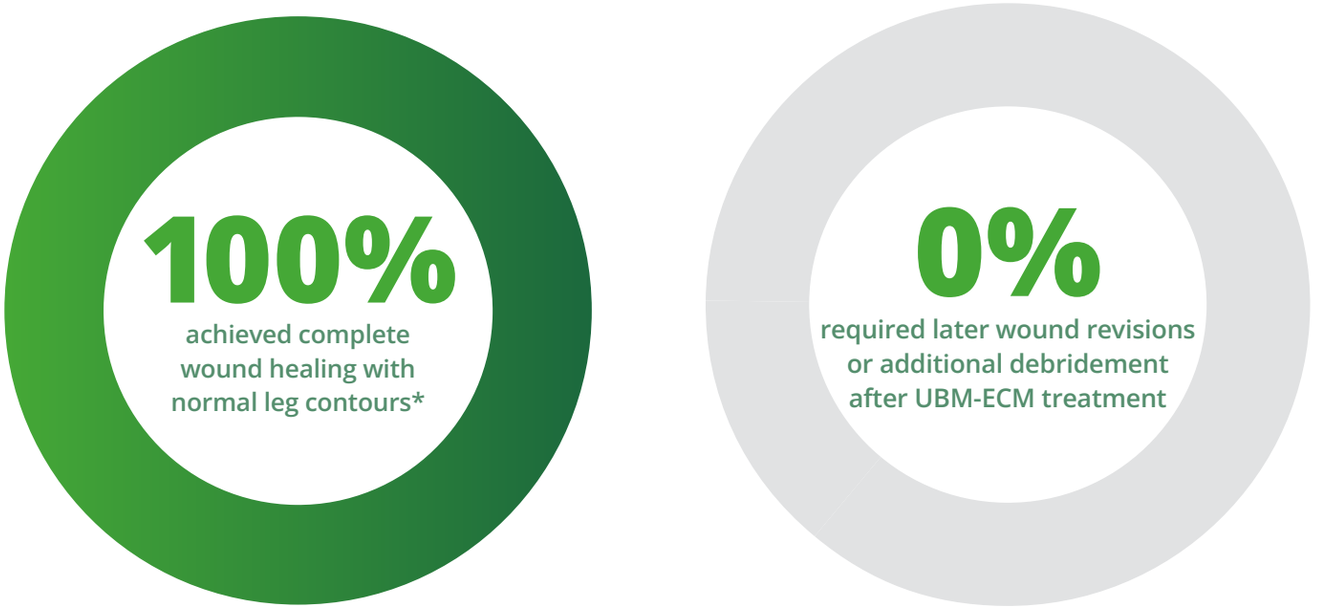
OBJECTIVE

To report the utility of UBM-ECM (MicroMatrix and/or Cytal) in managing open fracture wounds in patients who are poor flap candidates

BACKGROUND

- Management of open fractures of the distal lower extremity presents special challenges
- Delays in referral for wound closure affect treatment options
- Frame fixation can add challenges for wound access and for flap transfer
- Elderly and complex polytrauma patients may have to accept donor site defects

RESULTS



Healing achieved after a median of

1.7 APPLICATIONS

Mean: 2 applications; Range: 1-4

Mean time to complete healing

26.5 WEEKS

Median: 25 weeks; Range: 16-42

*In all living patients (8/9). One patient died during follow-up from causes unrelated to the use of UBM-ECM for wound care.

(continued)

Management of Open Distal Lower Extremity Wounds with Concomitant Fracture Using a Porcine Urinary Bladder Matrix

Kraemer BA, Geiger SE, Deigni OA, Watson TC; *Wounds,* 2016.

WOUND CARE SUMMARY

Subjects

- 4 open articular ankle fractures
- 5 open tibial fractures*
- All treated by the Plastic Surgery Service at St. Louis University
- Comorbidities:
  - Infection (7/8)
  - Smoking (5/8)
  - Arterial disease (3/8)
  - CAD (2/8)
  - Age ≥ 70 years (2/8)

Treatment

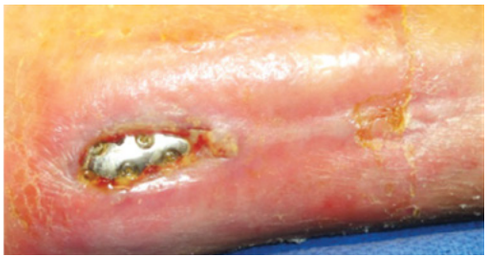
- Application of UBM-ECM followed by hydrogel† (6/9), NPWT (4/9), hydroconductive dressing‡ (2/9), or a burn dressing§ (1/9)
- Skin grafting STSG and/or FTSG (4/9)
- Follow-up: 10 to 36 months

ILLUSTRATIVE CASE STUDY

Open lateral ankle wound

A. Initial appearance.

B. Wound and product appearance during healing.



C. Week 31: sufficient healing to allow for plate removal.

KEY TAKEAWAYS

- The majority of wounds in this study were able to be closed via re-epithelialization or primary intention (6/11)
- MicroMatrix and/or Cytal Wound Matrix facilitated the establishment of a vascularized wound bed in which final wound closure was achieved via split- or full-thickness skin grafting (5/11)
- The devices facilitated successful closure of all 11 wounds without the need for complex reconstructive procedures, mitigating the risk of donor site morbidity, while also reducing physician time and hospital resources
- In contaminated wounds that had been cleaned and/or debrided, MicroMatrix and Cytal facilitated successful wound management

*2 of the 9 patients had 2 open wounds, for a total of ll wounds.

†Hydrogel (various manufacturers plus Tegaderm 3M Corporation, St. Paul, MN).

‡Drawtex (SteadMed Medical, Fort Worth, TX).

§Silverton Burn Dressing (Silverton, Argentum Medical, Geneva, IL).

The safety and effectiveness of concomitant use of Cytal and/or MicroMatrix with NPWT has not been established or cleared by the FDA.

Management of Open Distal Lower Extremity Wounds with Exposed Tendons Using a Porcine Urinary Bladder Matrix

Geiger SE, Deigni OA, Watson JT, Kraemer BA; *Wounds*, 2016.

Retrospective case series (N = 13)

OBJECTIVE

To report the utility of UBM-ECM (MicroMatrix and/or Cytal) in managing open distal LE wounds with exposed tendons in patients who are poor flap candidates

BACKGROUND

- Management of open fractures of the distal LE with exposed tendons presents special challenges
- Tendon mobility can lead to inflammation that impedes wound closure
- Use of pedicle or free flaps in the foot and ankle region often limits use of normal footwear and requires revisions

RESULTS

	Applications of UBM-ECM (median)	Time to healing in weeks (median)	Patients treated with STSG	Patients treated with suture
Achilles (n = 6)	1 (Mean: 1.2)	28 (Range: 7-78)	2	1
Tibialis anterior (n = 6)	2 (Mean: 1.83)	9 (Range: 6-18)	4*	-
Peroneus longus & brevis (n = 1)	7	14	-	1

THE AUTHORS OBSERVE THAT, IN THIS GROUP OF PATIENTS:

> "...UBM-ECM wound care needs are much simpler, there are few complications, and the patient heals with a limb...that permits use of regular footwear."

*1 patient underwent FTSG and STSG.

(continued)

Management of Open Distal Lower Extremity Wounds with Exposed Tendons Using a Porcine Urinary Bladder Matrix

Geiger SE, Deigni OA, Watson JT, Kraemer BA; *Wounds*, 2016.

WOUND CARE SUMMARY

Subjects

- Exposed tendons in wounds

6	6	1
Achilles	Tibialis anterior	Peroneus longus & brevis

- Not suitable candidates for local or free flaps
- All treated by the Plastic Surgery Service at St. Louis University
- Comorbidities: culture positive wounds (10/13), DM (5/13) smoking (4/13), venous stasis disease with edema (3/13), BMI > 35 (2/13)

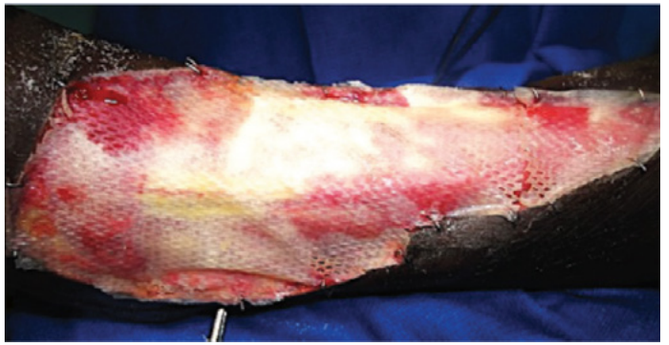
Treatment

- Debridement, application of UBM-ECM micronized powder (MicroMatrix); then application of UBM sheets (Cytal) to fill wound to skin level
- ABx (based on culture results) until tendons were not exposed
- Concomitant treatments included NPWT, hydrogels, petroleum gauze, and polyurethane covering
- Average F/U: 20 months (minimum: 13 months)

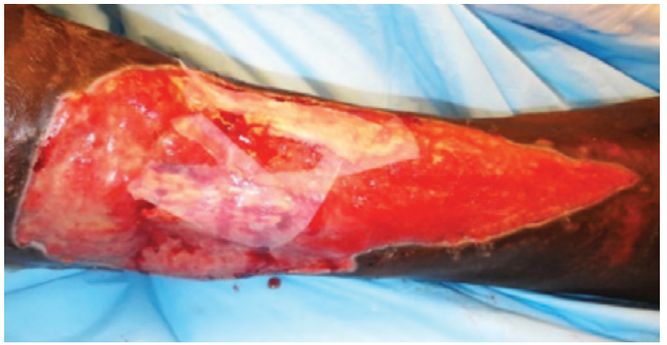
ILLUSTRATIVE CASE STUDY

Open LE wound after tissue necrosis from heroin injection

A. Initial appearance.



B. Healing with 2 applications of UBM-ECM and polyurethane sheet dressings.



C. Office treatment of residual wound with UBM-ECM sheets.

D. Wound healing after 3 months of hydrogel, prior to skin grafting.

KEY TAKEAWAYS

The devices facilitated the ability to successfully close all 13 wounds without the need for complex reconstructive procedures, mitigating the risk of donor site morbidity, while also reducing physician time and hospital resources. Furthermore, the devices allowed for simple wound management techniques and avoided prolonged and costly use of NPWT.

The safety and effectiveness of concomitant use of Cytal and/or MicroMatrix with NPWT has not been established or cleared by the FDA.

Extracellular Matrix Applications in the Treatment of Open Fractures with Complex Wounds and Large Soft Tissue Defects

Fokin AA, Puente I, Hus N, Rodriguez E, Weisz RD; *Journal of Orthopedic Trauma,* 2018.

Case series (N = 4; 5 injuries)

OBJECTIVE

To present 4 challenging cases involving the use of MicroMatrix and Cytal to manage open fractures with large soft tissue defects

BACKGROUND

- The traditional approach to the treatment of large extremity wounds involved flaps and an attempt at early wound closure
- Use of biological scaffolds such as ECM is a promising new trend in managing these types of wounds in orthopedic trauma care

CASE SUMMARIES

	PATIENT 1 21-year-old male	PATIENT 2 53-year-old male	PATIENT 3 53-year-old male	PATIENT 4 50-year-old female
Mechanism of Injury	Motorcycle accident	Run over by industrial lawn mower	Left arm struck telephone pole out of an open window	Jumped from moving car
Injuries	Open comminuted Grade IIIB fx of right tibia-fibula	• Multiple comminuted right LE Fxs • Avulsion injury right thigh and left heel pad	• Open grade IIIC floating elbow Fxs • Ischemia from brachial artery thrombosis	• Grade IIIB open Fx of left tibia-fibula, with severe degloving injury • Comminuted Fxs right metatarsals
Treatment Course	• Initial muscle flap became infected and was removed • Repeated applications of MicroMatrix/Cytal	• Immediate above-the-knee amputation • Repeated applications of MicroMatrix/Cytal to thigh and heel	• Multiple surgeries for vascular repair, debridement, skeletal fixation • 4 applications of MicroMatrix/Cytal	• Muscle flap to cover exposed tibia • 10 debridement procedures • 2 applications of MicroMatrix/Cytal
Wound Closure Procedure	STSG, 3 months after injury	STSG and cadaveric skin graft to thigh on Day 53 after trauma	STSG	STSG on Day 72 after injury

Outcome: Successful wound closure was achieved in **all 4 patients.**

> “Even in challenging cases where local flap coverage of bone or neurovascular structures is not possible, sequential xenograft implantation allowed us to achieve a stable soft tissue coverage.”

(continued)

Extracellular Matrix Applications in the Treatment of Open Fractures with Complex Wounds and Large Soft Tissue Defects

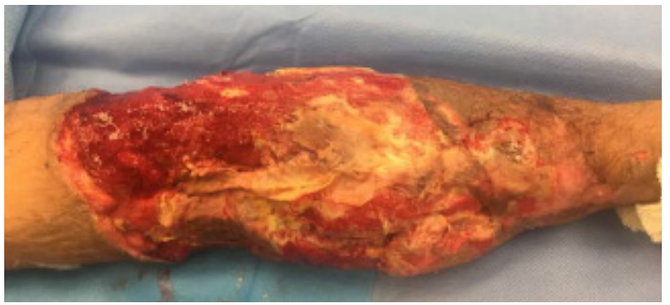
Fokin AA, Puente I, Hus N, Rodriguez E, Weisz RD; *Journal of Orthopedic Trauma,* 2018.

ILLUSTRATIVE CASE

Patient 3

Left arm struck telephone pole out of an open car window

A. Open comminuted fracture with a large soft tissue defect with exposed neurovascular structures at the antecubital fossa.



B. 2.5 weeks after injury: integration of the MicroMatrix/Cytal graft with development of granulation tissue.

C. Complete wound healing.

SURGICAL TECHNIQUE

For managing open extremity fractures with large soft tissue defects.

1. **Debridement of nonviable tissues**
2. **Copious irrigation**
3. **Skeletal stabilization**
4. **Application of MicroMatrix and/or Cytal**
   - Graft thickness based on wound depth and tissue deficit
   - Intent: fill the defect to skin level
   - Repeated over time as needed if defect depth requires additional bulk
5. **Secure graft with Mepitel® or Mepilex® Ag Mesh**
6. **NPWT**

KEY TAKEAWAYS

- MicroMatrix/Cytal applications supported successful closure in open comminuted extremity fractures with large soft tissue defects
- Use of MicroMatrix/Cytal did not impede use of orthopedic implants or other procedures such as additional debridement and internal/external fixation of fractures
- In cases of substantial soft tissue deficit, adequate tissue thickness can be achieved by applying additional Cytal over time—and without local rotational flap coverage

The safety and effectiveness of concomitant use of Cytal and/or MicroMatrix with NPWT has not been established or cleared by the FDA.

Porcine Bladder Extracellular Matrix for Closure of a Large Defect in a Burn Contracture Release

Mitchell KB, Gallagher JJ; *Journal of Wound Care*, 2012.

Case study

WOUND HISTORY

- 59-year-old man with a burn scar contracture
- Third-degree flame burn to neck treated with early excision and unmeshed skin grafts
- Month 10: local flaps reconstruction to relieve contractures
- Abscesses and sinus tracts developed in area of hypertrophic scar

WOUND CARE

- Month 17: hypertrophic scar removed; MicroMatrix and Cytal applied
- Biweekly moist dressing changes; weekly reapplication of MicroMatrix and Cytal

OUTCOME

- 16 weeks: complete wound closure
- Patient expressed great satisfaction with the functional and cosmetic result
- No recurrences of abscess or sinus formation

A. Sinus and fistula formation in mature, hypertrophic scar band.

B. Operative excision, leaving a large defect.

C. Week 16: definitive closure.

D. Week 16: definitive closure.

VANCOUVER SCAR SCALE

7 PRE-OP ⟶ **4** 6 MONTHS POST-OP

KEY TAKEAWAYS

- MicroMatrix and Cytal could serve a valuable role in burn reconstruction
- These devices may represent an option in chronic wounds that are difficult to close with traditional techniques

Chronic Wound Manangement

Evaluation of Tissue Engineering Products for the Management of Neuropathic Diabetic Foot Ulcers: an Interim Analysis

Frykberg RG, Cazzell SM, Arroyo-Rivera J, et al; *Journal of Wound Care,* 2016.

Prospective, randomized, comparative clinical trial (N = 95)

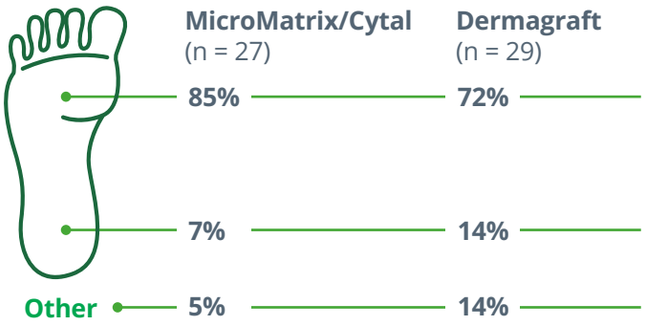
OBJECTIVE

Compare MicroMatrix and Cytal versus Dermagraft® in the treatment of nonhealing DFUs

SUBJECTS

All subjects had neuropathic DFUs. There were no significant differences between the treatment groups at randomization

WOUND LOCATION



METHODS

Conducted at 13 centers in the US

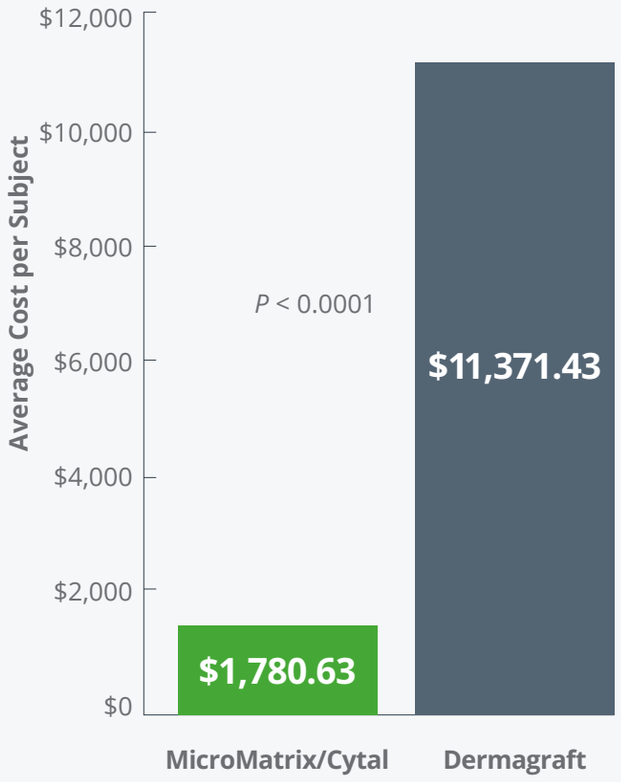
Treatments

- 4-week screening period
  - Subjects whose DFUs ↓ by ≤ 30% or ↑ by ≤ 50% entered the treatment phase
- 8-week treatment phase (or less, if DFU healed) with weekly device application
- 2-week SOC post-treatment

Outcome Assessment

- Wound characteristics, incidence of wound closure, rate of ulcer healing, QoL, cost-effectiveness, and recurrence rates (at 6 months)
- Blinded evaluator assessed wound closure
- This publication presents the planned interim results after half of the projected enrollment

COST



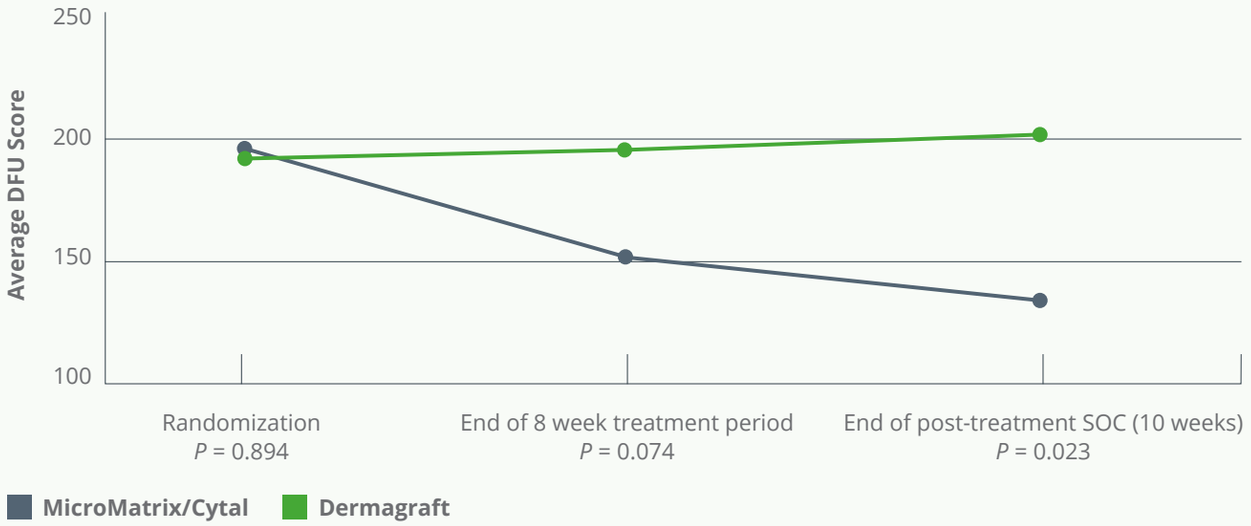
Evaluation of Tissue Engineering Products for the Management of Neuropathic Diabetic Foot Ulcers: an Interim Analysis

Frykberg RG, Cazzell SM, Arroyo-Rivera J, et al; *Journal of Wound Care,* 2016.

RESULTS

	MicroMatrix/Cytal (n = 27)	Dermagraft (n = 29)	*P*-value
Complete DFU closure, Day 56, n(%)	**5 (18.5%)**	**2 (6.9%)**	**0.244**
Change in wound size during 8-week treatment period (cm^2/8 weeks)	**-2.277**	**-0.792**	**0.762**
Complete DFU closure, Day 70, n(%)	**7 (25.9%)**	**9 (31.0%)**	**0.768**
Decrease in wound size during 8-week treatment period (cm^2/8 weeks)	**69.8 (+ 3.271)**	**65.7 (+ 1.910)**	**0.523**

QUALITY OF LIFE (based on DFU scores. Lower scores correlated with a more positive QoL assessment.*)



> **“…there is no statistical difference in efficacy between the two study products. However, the study results do show a significant cost difference and improvements in Quality of Life measurements for the patients managed with MicroMatrix/Cytal.”**

*The DFU is a validated QoL assessment. It consists of 58 items grouped in 11 lifestyle domains.

Urinary Bladder Matrix for the Treatment of Recalcitrant Nonhealing Radiation Wounds

Rommer EA, Peric M, Wong A; *Advances in Skin and Wound Care*, 2013.

Restrospective case series (N = 3)

OBJECTIVE

To report the authors experience in using UBM-ECM to treat chronic wounds that developed years after radiation therapy

BACKGROUND

- Radiation therapy often creates a non-vascularized tissue bed that resists healing
- Chronic wounds in previously irradiated tissue present treatment challenges

	Patient 1 64-year-old man	Patient 2 68-year-old woman	Patient 3 71-year-old woman
Dx **Reason for radiation Rx**	**Seminoma**	**Synovial sarcoma**	**Sacral sarcoma**
Wound location (year of radiation Rx)	**Abdomen** (1973)	**Anterior thigh** (1959)	**Presacral area*** (1996)
Previous management	• Healing by secondary intention • NPWT	• Local tissue flap • Skin graft • Fat injections • Regranex†Rx • NPWT	• Hyperbaric O_2 • Local tissue flap

*Complicated by pressure ulcer.

†Regranex Growth Factor Therapy (Healthpoint Biotherapeutics, Fort Worth, TX.)

The safety and effectiveness of concomitant use of Cytal and/or MicroMatrix with NPWT has not been established or cleared by the FDA.

(continued)

Urinary Bladder Matrix for the Treatment of Recalcitrant Nonhealing Radiation Wounds

Rommer EA, Peric M, Wong A; *Advances in Skin and Wound Care*, 2013.

ILLUSTRATIVE RESULTS

Patient 3

A. Initial defect.

B. Close-up of initial defect.

C. Debrided wound prior to attempted flap closure.

D. Wound breakdown, 8 weeks after flap procedure.

E. Completely healed wound at 19 months after wound management with UBM.

THIS RETROSPECTIVE STUDY WITH A SMALL SAMPLE SIZE:

> **“...demonstrates the safety and utility of UBM in aiding closure of chronic nonhealing wounds.”**

OUTCOME

After failing to close following wound management with multiple modalities, all wounds achieved closure after repeated applications of MicroMatrix and Cytal Wound Matrix.

Extending Limb Salvage After Fourth and Fifth Transmetatarsal Amputation in Diabetic Foot Infections Using ACell® Urinary Bladder Matrix

Underwood P, Cardinal P, Keller E, et al; *The American Surgeon*, 2020.

Retrospective case series (N = 2)

OBJECTIVE

To share experience in the use of ACell devices in avoiding further proximal amputation after fourth and fifth TMA in patients with wounds with exposed bone

BACKGROUND

- Limb salvage in DFI may improve QoL and function but is often limited by the depth of infection and tissue destruction
- Osteomyelitis is common in DFI and the loss of soft tissue makes it difficult to achieve bone coverage

PATIENT 1

42-year-old man with a DFI and osteomyelitis

WOUND TYPE

Polymicrobial DFI of the right foot requiring sequential resections of the fourth and fifth metatarsals

PMHx

DM and IHD

TREATMENT

MicroMatrix and Cytal Wound Matrix applied to attempt limb salvage; ABx, hyperbaric O_2

OUTCOME

F/U at 6.5 months: significant epithelialization with small (2 x 1.1 cm) residual opening

A. Initial appearance.

B. After multiple debridements and amputation of the fourth and fifth metatarsals.

C. 3 weeks following application of MicroMatrix and Cytal.

D. 7 weeks.

E. 3 months.

F. 6.5 months.

(continued)

Extending Limb Salvage After Forth and Fifth Transmetatarsal Amputation in Diabetic Foot Infections Using ACell® Urinary Bladder Matrix

Underwood P, Cardinal P, Keller E, et al; *The American Surgeon*, 2020.

PATIENT 2

70-year-old man with a DFI and osteomyelitis

WOUND TYPE

Gangrenous infection of the right foot, treated with ABx, resection of the fourth and fifth metatarsals and a posterior flap

PMHx

DM, HTN, dementia

TREATMENT

Application of MicroMatrix and Cytal Wound Matrix, ABx; reapplication of MicroMatrix and Cytal on Day 12

OUTCOME

F/U limited by COVID pandemic, but family reported that wound had healed

A. Initial appearance.

B. Appearance after multiple debridements and amputation of the fourth and fifth metatarsals.

C. 4 weeks following application of MicroMatrix and Cytal.

D. 7 weeks.

E. 3 months.

F. Picture of healed wound provided by patient's family.

> **"...Cytal Wound Matrix sheets combined with MicroMatrix powder appears a promising option in DFIs."**

A Value Analysis of Microsurgical Lower Extremity Reconstruction vs. Acellular Urinary Bladder Matrix (UBM) for Radiation Wounds of Lower Extremity

Micallef CJ, Johnson JN, Johnson MR; *Journal of Surgical Case Reports*, 2019.

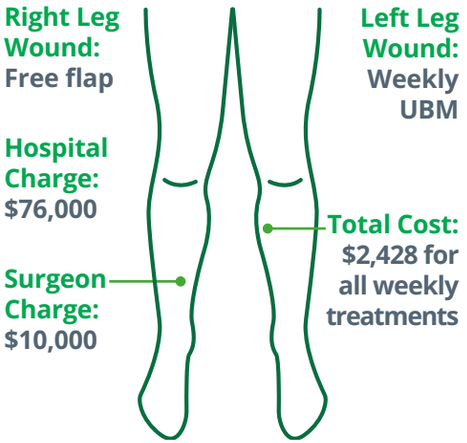
CASE REPORT

77-year-old man with a radiation wound to both LEs—and a value analysis

BACKGROUND

- Radiation therapy is an alternative to surgical treatment of non-melanoma skin cancers, but it can lead to recalcitrant radiation wounds
- These wounds may require flap reconstruction
- UBM grafts could be an alternative—eliminating the need for vascularized tissue transfer

COST COMPARISON



CASE SUMMARY

Wound History

- External beam radiation to both LEs for bilateral squamous cell cancer, leading to nonhealing ulcers
- Despite ABx Rx, pain and swelling worsened and draining ulcers developed
- Debridement with biopsy revealed a neutrophilic infiltrate, necrotic debris, and fibrinoid vascular changes suggestive of PG

Wound Care and Outcome

- Ulcers did not heal with local wound care, debridement, hyperbaric O_2
- Right LE: successfully treated with latissimus dorsi muscle flap and skin graft
- Left LE: managed for 2 years with wet to dry dressings, alginate silver, and an Integra Matrix product without success
- MicroMatrix and Cytal applied weekly to the left LE, led to complete wound closure and re-epithelialization within 7 weeks

A. Right LE with fully healed free latissimus dorsi flap coverage of radiation wounds.

B. Left LE with persistent nonhealing radiation wound after multiple courses of treatment (prior to wound management with UBM).

C. Healed Left LE 6 months after completion of wound management with UBM.

> **“...the use of porcine UBM in this patient eliminated the additional comorbidities and costs associated with undergoing a second free flap.”**

Health Economics & Outcomes Research

Complex Wounds Treated with MatriStem Xenograft Material: Case Series and Cost Analysis

Sasse KC, Ackerman EM, Brandt JR; *Open Access Journal of Surgery*, 2013.

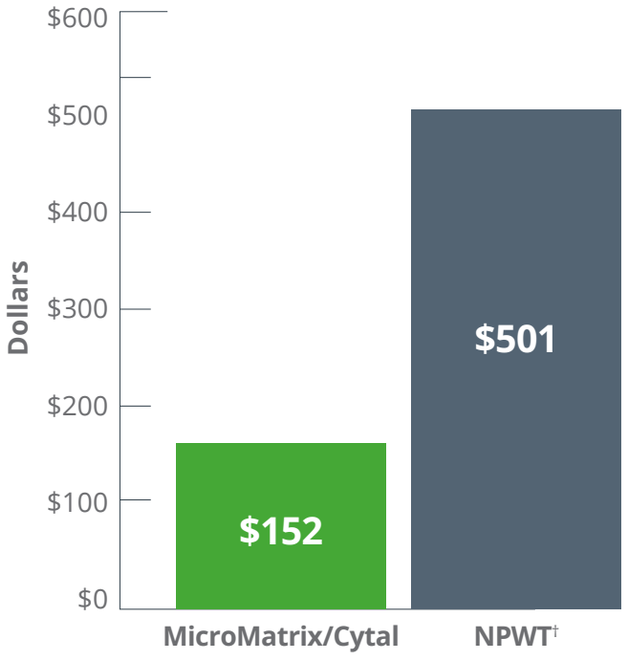
Case series (N = 10) and cost analysis

OBJECTIVE

To compare costs at a single institution of MicroMatrix/Cytal versus the costs of other treatment approaches in the management of complex wounds

RESULTS

Average (mean) cost of materials per week



Patient	Wound Location, Type	# of Grafts*	Total Material Cost ($)
1	Sacral ulcer, Stage IV	5	$2,508
2	Sacrococcygeal, pilonidal disease	7	$1,934
3	Abd wall, surgical wound dehiscence	14	$4,153
4	Abd wall, subfascial abscess	5	$2,219
5	Abd wall, complex abscess	14	$2,037
6	Ostomy closure	7	$1,935
7	Flank, soft tissue abscess	8	$1,864
8	Buttock, thigh, perirectal area, severe HS	10	$5,995
9	Scapula, S/P Rad Rx, leiomyosarcoma	10	$2,766
10	Ostomy closure	1	$825

*After initial graft procedure.

Results observed with MicroMatrix/Cytal without NPWT

100% of patients achieved **wound healing**

0% rate of wound infections or complications

11 weeks‡ median time to healing (Range: 4-33)

†Based on the size of the wounds in this patient series, the mean weekly cost of NPWT would initially be $583 and would decrease over time to $419 as the wounds became smaller; $501 is the blended average estimated cost.

‡The authors note that comparable healing times for these types of wounds might be required with NPWT but the study design did not include this type of estimate.

(continued)

Complex Wounds Treated with MatriStem Xenograft Material: Case Series and Cost Analysis

Sasse KC, Ackerman EM, Brandt JR; *Open Access Journal of Surgery*, 2013.

METHODS

Subjects

10 patients with a diverse set of complex wounds

Treatment

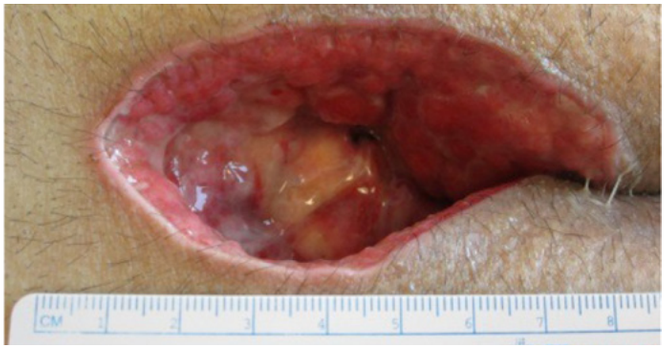
Weekly application of MicroMatrix and/or Cytal until wound healing was achieved

Cost Analysis

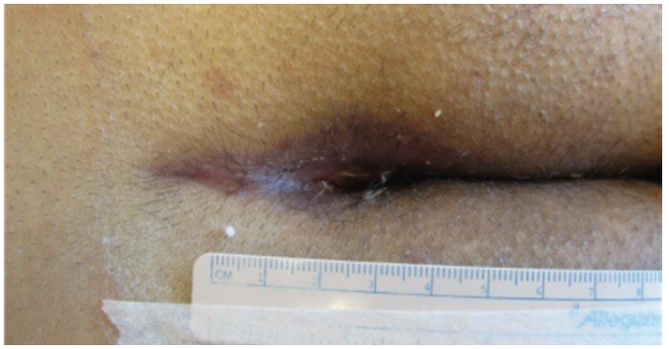
Calculation of the average cost of materials per week and comparison to historical costs of NPWT, based on the same contracted pricing agreements at the same institution

ILLUSTRATIVE CASE STUDY

27-year-old male with complex pilonidal disease and recurrent abscesses



A. Appearance of pilonidal wound intraoperatively.



B. Healed pilonidal wound following management with UBM.

KEY TAKEAWAYS

Treatment of diverse complex wounds with MicroMatrix/Cytal resulted in healing at lower costs compared to NPWT treatment, based on lower material costs and less need for wound care interactions with medical personnel.

The safety and effectiveness of concomitant use of Cytal and/or MicroMatrix with NPWT has not been established or cleared by the FDA.

A Comparative Analysis of Skin Substitutes Used in the Management of Diabetic Foot Ulcers

Martinson M, Martinson N; *Journal of Wound Care*, 2016.

Claims-based comparative cost analysis

OBJECTIVE

To compare relative product costs and clinical outcomes of 4 skin substitutes used to treat DFUs

METHODS

Data Set

Pts with DFUs who were treated with 1 of 4 types of skin substitutes were identified, using Medicare claims data from 2010 to 2014

Hero Analysis

- The analysis included 13,193 skin substitute treatment cases from 814 hospitals
- Devices were compared based on device utilization, costs, episode length, and amputation rate

PRODUCTS COMPARED

Cytal®
Porcine UBM

OASIS®
Porcine small intestinal submucosa

Apligraf®
Human keratinocytes and fibroblasts with bovine Type 1 collagen lattice

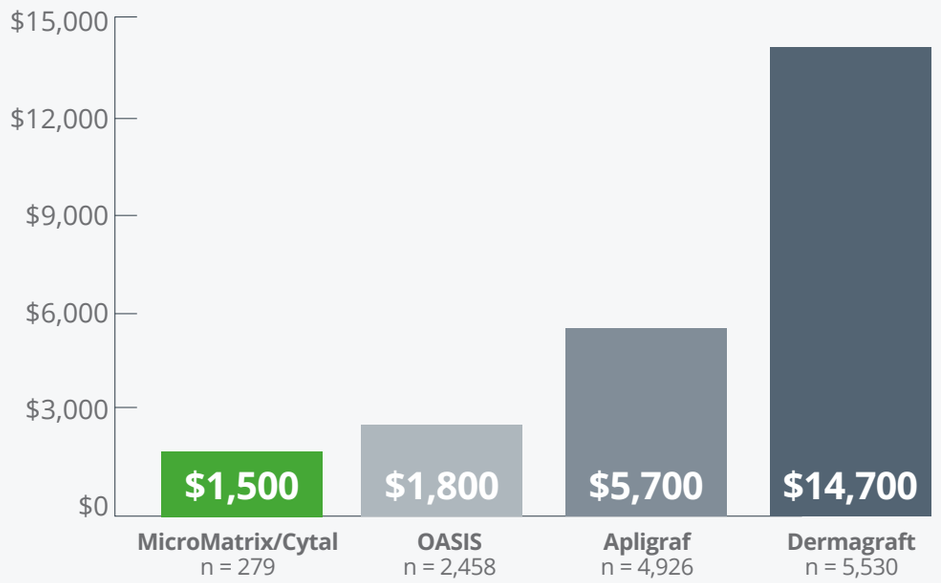
Dermagraft®
Human fibroblast-derived dermal substitute with bioabsorbable polyglactin mesh scaffold

RESULTS

Healing Rates*

- Healing rates were higher and episode durations were shorter for Cytal and OASIS than the other 2 devices
- Cytal use was greater in patients with osteomyelitis and gangrene, indicating that it was chosen for more complicated cases

Average Cost of Materials



KEY TAKEAWAYS

MicroMatrix/Cytal and OASIS were associated with shorter DFU episode lengths and lower treatment costs compared to Apligraf and Dermagraft.

*Based on rate of healing within 90 days.

The Science Behind Healing

31 **Modulation of Inflammation in Wounds of Diabetic Patients with Porcine Urinary Bladder Matrix.**
Paige JT et al. *Regenerative Medicine,* 2019.

Modulation of Inflammation in Wounds of Diabetic Patients with Porcine Urinary Bladder Matrix

Paige JT, Kremer M, Landry J, et al; *Regenerative Medicine*, 2019.

Prospective case control study (N = 18) and analysis of cellular infiltrate during wound healing

OBJECTIVE

To determine whether the macrophage phenotype-related gene expression after management with MatriStem UBM would differ in diabetic patients compared to nondiabetic patients

BACKGROUND

Macrophages mediate wound healing and exist in many phenotypes

M1 Macrophage

- Proinflammatory
- Clears pathogens and damaged tissue

M2 Macrophage

- Promotes wound healing
- Decreases inflammation

The M1:M2 Score

- Ratio associated with the degree of wound inflammation
- Can be determined via relative gene expression
- In pts with DM, the M1:M2 score is increased, which can delay wound healing

METHODS

Subjects

N = 18 (9 diabetic and 9 nondiabetic) with non-clinically infected open wounds not previously treated with a biologic scaffold

TREATMENT AND M1:M2 ASSESSMENT

- Wound debridement samples obtained just before application of UBM (MicroMatrix, Cytal, or both)
- Second debridement samples obtained 7 to 14 days after UBM application
- Wound area reduction measured at time of second debridement
- Relative gene expression associated with M1 and M2 macrophage phenotypes were measured

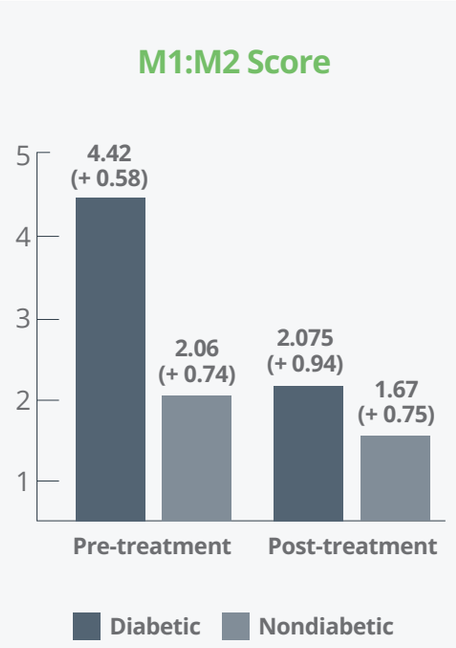
RESULTS

- DM pts had a significantly higher M1:M2 ratio pre-treatment compared to post-treatment
- Following application of MicroMatrix and/or Cytal, the M1:M2 ratio was reduced to similar levels in both DM and non-DM subjects
- M1:M2 scores correlated with the rate of wound area reduction

UBM was associated with wound size reduction in both groups:

DM Subjects
35% (± 14%)

Non-DM Subjects
43% (± 18%)



KEY TAKEAWAYS

UBM has the potential to restore a normal inflammatory response in diabetic patients, suggesting that management with UBM in diabetic patients may result in healing rates similar to nondiabetic patients.

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CHRONIC WOUND MANAGEMENT

Evaluation of Tissue Engineering Products for the Management of Neuropathic Diabetic Foot Ulcers: An Interim Analysis.
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Rommer EA, Peric M, Wong A. *Adv Skin Wound Care*. 2013;26 (10):450-455.Retrospective case series (N = 3)

Extending Limb Salvage After Fourth and Fifth Transmetatarsal Amputation in Diabetic Foot Infections Using ACell® Urinary Bladder Matrix.
Underwood P, Cardinal P, Keller E, et al. *Am Surg.* 2020. doi:10.1177/0003134820973730. Epub ahead of print.
Retrospective case series (N = 2)

A Value Analysis of Microsurgical Lower Extremity Reconstruction vs. Acellular Urinary Bladder Matrix (UBM) for Radiation Wounds of the Lower Extremity.
Micallef CJ, Johnson JN, Johnson MR. *J Surgi Case Rep*. 2019;2019(3):rjz051. doi:10.1093/jscr/rjz051.
Case report: 77-year-old man with a radiation wound to the LE—and a value analysis

HEALTH ECONOMICS AND OUTCOMES RESEARCH

Complex Wounds Treated with MatriStem Xenograft Material: Case Series and Cost Analysis.
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Case series (N = 10) and cost analysis

A Comparative Analysis of Skin Substitutes Used in the Management of Diabetic Foot Ulcers.
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Claims-based comparative cost analysis

THE SCIENCE OF HEALING

Modulation of Inflammation in Wounds of Diabetic Patients with Porcine Urinary Bladder Matrix.
Paige JT, Kremer M, Landry J, et al. *Regen Med*. 2019;14(4):269-277.
Prospective case control study (N = 18) and analysis of cellular infiltrate during wound healing

MicroMatrix®

INDICATIONS FOR USE: MicroMatrix is intended for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears), and draining wounds. The device is intended for one-time use.

CONTRAINDICATIONS: Contraindicated for use on patients with known sensitivity or allergy to porcine materials or third-degree burns.

WARNINGS:

- If active infection is present, treat patient to resolve infection prior to device application.
- Do not use glass vial if cracked, broken, or otherwise damaged.
- MicroMatrix is not indicated for treatment of alopecia.

PRECAUTIONS: Do not tap glass vial with metal objects or handle in a way that may cause glass to break and contaminate wound.

Cytal® Wound Matrix

INDICATIONS FOR USE: Cytal Wound Matrix is intended for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears), and draining wounds. The device is intended for one time use.

CONTRAINDICATIONS:

1. Patients with known sensitivity or allergy to porcine materials.
2. Third-degree burns.

WARNINGS:

- Exposure to contaminated or infected field can lead to rapid breakdown of device.
- If active infection is present, treat patient to resolve infection prior to device application.
- Do not use if cracked, broken, or otherwise damaged.

PRECAUTIONS: Always use aseptic technique when handling device.

Integra® Bilayer Wound Matrix

INDICATIONS FOR USE: Integra Bilayer Wound Matrix is indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

CONTRAINDICATIONS: This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials. This device is not indicated for use in third-degree burns.

INTEGRA®